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Spaying and urinary incontinence in bitches under UK primary veterinary care: a case–control study

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OBJECTIVES: To evaluate associations between spaying and urinary incontinence in bitches under primary veterinary care in the UK.

MATERIALS AND METHODS: A case–control study was nested within the study population of 333,910 bitches, which included all bitches within the VetCompass database with an electronic patient record in 2016 or in both 2015 and 2017. The electronic records were searched automatically for urinary incontinence cases, which were manually reviewed for inclusion. All non-cases were included as controls. Additional demographic and clinical information was extracted on cases and controls.

RESULTS: The study included 427 incident cases and 1708 controls that were presented between November 1, 2014 and October 31, 2017. Prior spaying was associated with increased odds of urinary incontinence (odds ratio: 3.01; 95% CIs: 2.23 to 4.05). Increased odds of urinary incontinence were additionally associated with increasing age and increasing bodyweight. Age at spay was not associated with urinary incontinence.

CLINICAL SIGNIFICANCE: The findings support spaying as a major risk factor associated with urinary incontinence, but age at spay appears to be of less clinical importance. These results will help assist clinicians in making evidence-based recommendations on spaying while taking other considerations for urinary incontinence into account.

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INTRODUCTION

Urinary incontinence (UI) is defined as the involuntary escape of urine during the storage phase of micturition (Schaer 2010). Bitches usually present either as juveniles with congenital incontinence or as adults with acquired incontinence (Holt 1990). In one study, juvenile incontinent bitches were defined as those in which incontinence had been noted at birth or soon after acquisition as a puppy (under 6 months old), and adult incontinent bitches were those that were continent as puppies but developed UI later in life (Holt 1985). However, it is possible that adult bitches may also present with delayed-onset UI that has a

congenital aetiology (Thomas & Yool 2010). The most common cause of UI in juvenile bitches is ureteral ectopia, a congenital condition in which one or both ureteral orifices are located distal to the trigone of the bladder (McLoughlin & Chew 2000). Urethral sphincter mechanism incompetence (USMI) is the most commonly reported cause of UI in adult bitches (Holt & Thrusfield 1993).

Ideally, diagnostic confirmation of UI should begin with a complete history, physical examination, serum biochemistry, urinalysis and urine culture, followed by appropriate imaging studies to determine the precise cause of the UI (Silverman & Long 2000). In primary care practice, a presumptive diagnosis of USMI is often made in adult bitches based on the signalment,

history, physical examination, urinalysis (+/- urine culture) and response to USMI-specific treatment without further investigation (Gregory 1994, Silverman & Long 2000). As a presumptive diagnosis of USMI is often made, here we refer to UI overall rather than to precise subsets to avoid assumptions regarding causality.

The prevalence and incidence of UI has been reported at differing frequencies but with a general trend towards higher proportions of spayed bitches affected than entire bitches. In one study, 20.1% of spayed bitches were described as being affected (Arnold 1997). Overall UI prevalence has been estimated at 3.14% in primary care practice in England (O'Neill *et al.* 2017). In a cohort study following bitches from 12 weeks old, 5.20% of spayed bitches and 1.01% of entire bitches developed UI within the 5-year follow-up period (Thrusfield *et al.* 1998).

USMI, the major cause of UI in adult bitches, has a complex and poorly understood pathophysiology. Anatomical, hormonal and neurological abnormalities may all play a role in the development of USMI (Gregory 1994, Coit *et al.* 2008, de Bleser *et al.* 2011). An association between spaying and an increased risk of developing USMI has been widely reported (Holt 1985, Holt & Thrusfield 1993, Thrusfield *et al.* 1998, O'Neill *et al.* 2017), although the evidence supporting this association was identified as weak in a systematic review (Beauvais *et al.* 2012).

Although the pathophysiological mechanisms behind associations between spaying and UI are not fully elucidated, there is evidence of a direct or indirect relationship between continence and gonadotrophin concentrations (Reichler *et al.* 2005). Gonadotrophins, along with oestrogen, may be involved in regulating bladder tone and maintaining urethral wall thickness, thus creating a more efficient urethral seal (Ponglowhapan *et al.* 2007). A reduction in gonadotrophin receptors, specifically luteinising hormone (LH) and follicle-stimulating hormone (FSH), and cyclooxygenase-2 (COX-2) receptors has been reported in spayed bitches. Bladder tone and micturition reflexes are regulated by LH and FSH, with their production mediated by COX-2 (Ponglowhapan *et al.* 2007, Ponglowhapan *et al.* 2008a). Thus, a reduction in receptors may reduce bladder tone and negatively influence micturition reflexes.

Associations between the age at spay and later development of UI have been investigated, with some weak evidence that UI risk in the bitch decreases as the age at spay increases up to 12 months of age; there is no evidence of an effect after this age (Spain *et al.* 2004, Beauvais *et al.* 2012). A recent USA study reported that bitches weighing >25 kg that were spayed within their first year of life had a decreased hazard of UI for every 1-month delay in spaying. For a 25 kg dog, a 1-month delay in ovariohysterectomy age decreased the hazard of incontinence by 11%. On the other hand, the hazard of UI did not significantly change with increasing age at spay for dogs <15 kg (Byron *et al.* 2017).

Release of LH and FSH is controlled by Gonadotrophin Releasing hormone (GnRH), therefore GnRH analogues have been evaluated for efficacy in the treatment of UI (Donovan and others 2014, Reichler *et al.* 2003, Reichler *et al.* 2006). After 5 weeks of treatment with a GnRH analogue, the frequency of UI was reduced by 71% in affected bitches (Reichler *et al.* 2006).

The effect of GnRH immunisation as a treatment for USMI was recently evaluated. Continence was only maintained in 44% of bitches, with side effects reported in 90% of bitches (Donovan *et al.* 2014). Therefore, further evaluation of the role gonadotrophins play in the development of UI, and the use of GnRH analogues as a treatment for UI is warranted.

Further work identified that gonadectomised dogs had a higher proportion of collagen and reduced glycosaminoglycan (GAG) components in the lower urinary tract (LUT) compared to intact dogs. These changes in neutered dogs may compromise structural and functional integrity of the LUT and are possibly involved in the underlying mechanism of UI post spaying (Ponglowhapan *et al.* 2008b, 2011).

An association between timing of spay relative to first oestrus and development of UI in the bitch remains unclear. One Swiss study reported lower UI risk in early spayed bitches compared with bitches spayed after first oestrus (Stocklin-Gautschi *et al.* 2001). In contrast, a UK study reported evidence of increased risk of acquired UI when bitches were spayed before, rather than after, their first oestrus (Thrusfield *et al.* 1998). A systematic review evaluating this conflicting information identified no evidence of an association between UI and the occurrence of oestrus before spay (Beauvais *et al.* 2012).

Breed and body size have been reported as risk factors for UI, with a recent UK study reporting the highest odds in the Irish setter, Dobermann, bull mastiff, rough collie, Dalmatian and boxer (O'Neill *et al.* 2017). These results are similar to earlier reports, with the old English sheepdog, Rottweiler and Weimaraner additionally reported to be at high risk (Holt & Thrusfield 1993). A significant association has been found between bodyweight and risk of UI (de Bleser *et al.* 2011, O'Neill *et al.* 2017), with one study reporting that larger dogs (>15 kg) are approximately seven times more likely to develop acquired UI compared with small dogs (<15 kg) (Forsee *et al.* 2013). Age has been identified as a significant risk factor, with an increase in age associated with an increased risk of UI (Thrusfield *et al.* 1998, Stocklin-Gautschi *et al.* 2001, de Bleser *et al.* 2011, O'Neill *et al.* 2017). Obesity, although not shown to cause USMI, is believed to worsen the severity of UI (Johnston. and Johnston & Tobias 2017). One study reported bitches that were overweight before spaying as being at 3.5 times the risk of developing the condition compared with subjects that were not overweight before and after surgery (Angioletti *et al.* 2004).

Using veterinary clinical data from the VetCompass™ Programme (VetCompass 2017), this study aimed to further explore the association between all-cause UI and spay status, age at spay and spay relative to first oestrus. Veterinarians have mentioned UI as one of the main contraindications for spaying bitches, second only to obesity (Diesel *et al.* 2010). Conflicting veterinary advice is often given regarding spaying practices, with mixed views on whether bitches should be spayed at all and, if so, whether they should be spayed before or after first oestrus (Diesel *et al.* 2010). UI has been reported to cause unfavourable outcomes in 10 to 20% of affected households, with owners describing feelings of anger and frustration (de Bleser *et al.* 2011) and with euthanasia of the affected animal considered in certain circumstances

(Holt 1983, O'Neill *et al.* 2017). The direct welfare impact on the bitch includes an increased risk of urinary tract infection and urine scald (Diesel *et al.* 2010). Therefore, due to the welfare implications for the bitch, the potential impact on the owner–animal bond, the cost of any prescribed treatment and the importance of the condition in the spaying decision-making process, further evaluation of the condition and the role spaying plays in the development of UI is warranted.

METHODS

The VetCompass™ Programme collects anonymised electronic patient record (EPR) data from primary care veterinary practices in the UK for epidemiological research (VetCompass 2017). Collaborating practices can record summary diagnosis terms during a period of care from an inbuilt VeNom Code list (The VeNom Coding Group 2017). Information available for VetCompass™ researchers includes a unique ID for each animal with additional species, breed, date of birth, gender, spay status and bodyweight. Clinical information from free-text clinical notes, summary diagnosis terms (VeNom codes), treatment and deceased status with corresponding dates are also available. Ethics approval was obtained from the RVC Ethics and Welfare Committee for this study (reference number 2015/1369).

A nested case–control study design was used to explore associations between spaying and UI. The denominator population in which the case–control study was nested included all bitches in the VetCompass™ database with an EPR in 2016 or EPRs in both 2015 and 2017 to indicate they remained actively registered with the practice in 2016. Power calculation estimated that approximately 90 cases and 360 controls were required to identify if spayed bitches had at least twice the odds of UI compared with entire bitches, assuming 80% power and 95% CI (CDC 2015). A 1:4 case: control ratio was used as statistical power was unlikely to substantially increase above this ratio (Dohoo 2010).

Inclusion criteria for a UI case were as follows: (1) a final diagnosis of UI (or synonym) recorded in the EPR; and/or, (2) treatment with either phenylpropanolamine or oestriol. Exclusion criteria included: UI recorded as occurring secondary to a primary neurological condition, evidence of urinary tract infection with UI reported to resolve with appropriate treatment of the infection or evidence that the phenylpropanolamine or oestriol was given for a reason other than UI.

Incident cases only were included in the study, with these cases defined as those bitches that were first presented for UI between November 1, 2014 and October 31, 2017. Potential cases were identified using search terms in the clinical notes (incont*, usmi, urin* leak*, incompet*, nocturia, urethral sp*, wetting, wet* bed, drib* urin*, inapprop* urin*) and treatment fields (propan*, incuri*, urilin, enurace) relevant to the diagnosis and management of UI. The search findings were merged, and a random subset of these candidate cases had their clinical notes examined manually in detail to identify if they met the case definition. The remaining non-candidate bitches were classified as non-cases and were available for inclusion as controls. The non-candidate

bitches were entered into the study and randomly ordered for assessment. The EPRs of the randomly selected controls were examined manually in detail to ensure there was no evidence of UI. Demographic data for cases and controls were extracted automatically from the VetCompass™ database, with further data relating to spay and UI extracted manually from the EPR.

The age (years) at diagnosis of cases was calculated at the date of first diagnosis of UI. The age of controls was calculated at the end date of the study period (October 31, 2017), by which point these bitches had not become cases. Consistent with previous literature in the subject area (O'Neill *et al.* 2017), age was categorised as quintiles (years): <3, 3 to <6, 6 to <9, 9 to <12 and ≥12. Bitches were categorised into a “Breed” variable using standardised breed terms. In order to maintain sufficient power for analysis, the Breed variable included specific breeds with at least five cases of UI and/or breeds with at least 30 animals overall. The remaining bitches were grouped into to “Purebred – Other”, “Crossbred – designer” (including labradoodles, cockapoos and so forth) or “Crossbred – non-designer”. Spay status was categorised as “Spayed” and “Entire”, with the status taken at the date of UI diagnosis for cases and the end of study period for controls. Therefore, any cases spayed after being first presented with UI were considered entire in the analysis. Bodyweight (kg) described the closest recorded value to the age at diagnosis (for cases) and bodyweight at the end of the study period (for controls). Based on previous literature in the subject area (O'Neill *et al.* 2017), bodyweight (kg) was categorised in quartiles: < 10, 10 to <20, 20 to <30 and ≥30, with missing values grouped as “Not recorded”. Non-adult bodyweights were included in the study as risk factors at the point of UI diagnosis were of primary interest. Veterinary group attended was categorised as 1 to 3 based on the three practice groups involved in the study.

Age at spay (months) was calculated at the date of spay surgery and categorised into quartiles: <6, 6 to <12, 12 to <24 and ≥24. Spay relative to oestrus was recorded as “pre first oestrus” and “post first oestrus”. Missing data for timing of spay and spay relative to oestrus were classified as “Not recorded” for those spayed but with insufficient evidence of timing and relation to oestrus. Data for spay relative to oestrus were collected but were not carried forward for analysis due to the limited recording of spay relative to oestrus. Remaining data were checked and cleaned in Excel (Microsoft Corp) before export to SPSS version 24.0 (IBM Corp) for statistical analysis.

Descriptive statistics were generated for UI cases and controls. Continuous variables were summarised using median, interquartile range (IQR) and range. Binary logistic regression modelling was used to evaluate univariable associations between the two risk factors of primary interest (spay status and age at spay) and UI diagnosis. Additional variables were also assessed as potential confounders: age, breed, bodyweight and vet group. Explanatory variables with liberal univariable association with a diagnosis of UI ($P < 0.2$) were carried forward for multivariable logistic regression modelling.

Separate multivariable modelling evaluated the two risk factors of primary interest (“Spay status” and “Age at spay”) in conjunction with the potential confounders. Multivariable modelling for “Spay status” used the entire dataset, whereas multivariable

modelling for “Age at spay” used only the spayed subset because this variable did not apply to entire bitches. Model building used a backwards stepwise approach, with “Vet group” included as a fixed effect to adjust for clustering at the clinic level. Potential confounders were assessed by checking for a marked change in the odds ratio (OR) after removal of the variable from the model. Collinearity was investigated by examining the variance inflation factor (VIF) and tolerance, with collinearity indicated if $VIF > 10$ and tolerance < 0.1 (Myers 1990, Menard 1995). Model fit was assessed using the Hosmer–Lemeshow Test and by calculating the area under the Receiver operating characteristic (ROC) curve (Hosmer & Lemeshow 2000).

The study denominator population of 333,910 bitches yielded 14,170 candidate UI cases. Of the candidates, 2077 (14.7%) were manually checked, with 427 (20.6% of those checked) meeting the case definition as an incident UI case from November 1, 2014 to October 31, 2017. The remaining 319,740 non-candidate bitches (with no evidence of UI in the search terms) were classified as non-cases and were available for inclusion as controls, of which 1708 were randomly selected (1:4 case: control ratio) and manually checked, with no false negatives identified.

RESULTS

Data completeness for the cases and controls were: breed 99.9%, age 100.0%, spay status 100% and bodyweight 79.4%. Data completeness for the spayed subset of cases and controls were: age at spay 45.4% and spay relative to oestrus 23.1%. Due to the limited recording of spay relative to oestrus, this variable was not carried forward for further analysis.

Descriptive analysis included 427 incident UI cases and 1708 controls. The median age at UI diagnosis was 9.1 years (IQR 5.1 to 12.3, range 0.3 to 18.4), with the median age of controls being 5.2 years (IQR 2.7 to 8.6, range 1.0 to 20.0). Median bodyweight at first diagnosis of UI was 19.8 kg (IQR 11.2 to 27.5, range 2.1 to 71.3), with the median bodyweight of controls being 12.8 kg (IQR 7.3 to 23.0, range 1.1 to 76.0). Of the cases, 82.4% (352) were spayed compared with 52.8% (901) of the controls. The most common breeds amongst cases were the Labrador retriever (6.8%; 29), Border collie (6.6%; 28), English springer spaniel (5.4%; 23) and Jack Russell terrier (5.2%; 22) in addition to 135 (31.6%) non-designer crossbreeds. The most common breeds amongst controls were the Staffordshire bull terrier (7.2%; 123), Jack Russell terrier (6.3%; 107), Labrador retriever (6.2%; 106) and Chihuahua (4.0%; 69) in addition to 407 (23.8%) non-designer crossbreeds. Breed information was missing for two dogs.

Of the spayed animals, the age at spay was available for 30.1% (106) cases and 51.4% (463) controls. Median age at spay was 14.5 months (IQR 7.0 to 32.9, range 5.0 to 193.8) for cases and 15.2 months (IQR 7.0 to 31.9, range 2.8 to 134.6) for controls. Information on whether spay was performed before or after first oestrus was not available within the records for 84.9% (299) cases and 73.7% (664) controls (*i.e.* spaying had been carried out before the first available EPR, and the records held no

information on the timing of spay relative to first oestrus). Therefore, this variable was not included in the analysis.

Risk factors for UI diagnosis

Spay status

Univariable logistic regression using the whole dataset identified five variables that were carried forward for multivariable modelling to assess “Spay status” as a risk factor for UI: spay status, age, bodyweight, breed and vet group (Table 1). The final multivariable model retained all five variables (Table 2). After accounting for the other confounding factors, spayed bitches had 3.01 (95% CI: 2.23 to 4.05) times the odds of UI compared with entire bitches. Age, breed and bodyweight were included in the model as confounders, but these results are also reported. Four breeds had increased odds of UI compared with non-designer crossbreeds: Hungarian vizsla (OR: 11.40; 95% CI 1.43 to 90.97), Dobermann (OR: 6.44; 95% CI 1.13 to 36.60), Weimaraner (OR: 5.83; 95% CI 1.25 to 27.28) and boxer (OR: 2.98; 95% CI 1.23 to 7.18). The shih-tzu (OR: 0.12; 95% CI 0.02 to 0.89), Staffordshire bull terrier (OR: 0.20; 95% CI 0.10 to 0.41) and Labrador retriever (OR: 0.54; 95% CI 0.32 to 0.91) showed reduced odds. Bitches aged 3.0 to < 6.0 years had reduced odds of UI compared with those aged < 3.0 years (OR: 0.64; 95% CI 0.42 to 0.99). Bitches aged 9.0 to < 12.0 years and those ≥ 12.0 years had increased odds of UI compared with those aged under 3.0 years (OR: 1.67; 95% CI 1.09 to 2.55 and OR: 4.06; 95% CI 2.64 to 6.24, respectively). Increasing bodyweight (kg) was associated with increased risk of UI; bitches weighing ≥ 30.0 had 3.18 (95% CI 1.98 to 5.12) times the odds of UI compared with those < 10.0 . The Hosmer–Lemeshow test indicated no evidence of poor model fit ($P = 0.189$), and the area under ROC curve (0.819) indicated good predictive ability.

Age at spay

Univariable logistic regression using the spayed-only subset identified five associated variables that were carried forward for multivariable modelling to assess “Age at spay” as a risk factor for UI: age at spay, age, bodyweight, breed and vet group (Table 3). The final multivariable model retained all five variables, with the results for “Age at spay” presented in Table 4. The Hosmer–Lemeshow test indicated no evidence of poor model fit ($P = 0.178$), and the area under ROC curve (0.778) indicated good predictive ability. After accounting for the effects of the confounding variables, bitches without an age at spay recorded had increased odds of a UI diagnosis (OR: 2.60; 95% CI 1.40 to 4.85).

DISCUSSION

A case–control study including 2135 bitches was nested within the overall study population of 333,910. This was an exploratory study and was not hypothesis driven; therefore, individual category P -values were removed in the multivariable analysis as a suggestion was made that their use can be misleading and can

Table 1. Descriptive statistics and univariable logistic regression results for risk factors associated with the incidence of urinary incontinence in bitches under primary veterinary care in the UK (n=2135)

Variable	Category	Control	Case	Odds ratio	95% CI	Variable P-value
Spay status	Entire	807	75	Base		<0.001
	Spayed	901	352	4.20	3.22 to 5.49	
Age (years)	<3.0	471	50	Base		<0.001
	3.0 to <6.0	489	67	1.29	0.88 to 1.90	
	6.0 to <9.0	369	89	2.27	1.57 to 3.30	
	9.0 to <12.0	236	106	4.23	2.92 to 6.13	
	≥12.0	143	115	7.58	5.18 to 11.09	
Bodyweight (kg)	<10.0	514	86	Base		<0.001
	10.0 to <20.0	369	124	2.00	1.48 to 2.73	
	20.0 to <30.0	251	121	2.88	2.10 to 3.95	
	≥30.0	151	80	3.12	2.22 to 4.51	
Breed	Not recorded	423	16	0.23	0.13 to 0.39	<0.001
	Crossbreed – non-designer	407	135	Base		
	Hungarian vizsla	2	6	9.04	1.80 to 45.34	
	Weimaraner	3	7	7.04	1.79 to 27.59	
	Dobermann	3	5	5.03	1.19 to 21.3	
	Boxer	14	14	3.02	1.40 to 6.49	
	Border collie	41	28	2.06	1.23 to 3.46	
	German shepherd dog	30	18	1.81	0.98 to 3.35	
	English springer spaniel	42	23	1.65	0.96 to 2.85	
	West Highland white terrier	35	12	1.03	0.52 to 2.05	
	Labrador retriever	106	29	0.83	0.52 to 1.30	
	Bichon frise	22	6	0.82	0.33 to 2.07	
	Cavalier King Charles spaniel	42	11	0.79	0.40 to 1.58	
	Jack Russell terrier	107	22	0.62	0.38 to 1.02	
	Cocker spaniel	67	13	0.59	0.31 to 1.09	
	Purebreed – other	347	64	0.56	0.40 to 0.77	
	Yorkshire terrier	56	10	0.54	0.27 to 1.09	
	Crossbreed – designer	101	10	0.30	0.15 to 0.59	
	Staffordshire bull terrier	123	10	0.25	0.13 to 0.48	
	French bulldog	32	2	0.19	0.05 to 0.80	
	Shih-tzu	57	1	0.05	0.01 to 0.39	
	Chihuahua	69	1	0.04	0.01 to 0.32	
	Not recorded	2	0			
Vet group	1	994	289	Base		0.002
	2	705	137	0.67	0.53 to 0.84	
	3	9	1	0.38	0.05 to 0.362	

lead to misinterpretation of data (Chakkera *et al.* 2016). Spayed bitches had increased odds of UI diagnosis compared with entire bitches, while there was no clear trend between age at spay and UI diagnosis. Data availability in the clinical records on spay relative to oestrus was limited and so this variable was not included in multivariable analysis.

Consistent with previous work, the multivariable models identified increased odds of UI diagnosis in heavier and older bitches and in particular breeds, including the Hungarian vizsla, Dobermann, Weimaraner and boxer.

Spaying was identified as a risk factor in the multivariable analysis, which is in agreement with previous findings (Thrusfield 1985, Holt & Thrusfield 1993, Thrusfield *et al.* 1998, O'Neill *et al.* 2017). In the current study, spayed bitches had 3.01 times the odds of UI compared with entire bitches. Previous studies have reported ORs of 16.9 (63 cases) and 14.7 (41 cases), respectively, but these studies were focused solely on therapeutically responsive USMI as a cause of UI, and the number of cases included were relatively small (Thrusfield 1985, Holt & Thrusfield 1993). A more recent study with a larger number of UI cases and with a similar case definition to the current study reported that spayed bitches had 2.23 times the odds of UI diagnosis compared with

entire bitches (O'Neill *et al.* 2017). The slightly higher estimate in the current study may be because the issue of temporality was addressed – *i.e.* the spayed status of the bitch was recorded at the time of diagnosis of UI, whereas the earlier study reported the spay status of cases and non-cases at the final EPR, with some bitches potentially being spayed after diagnosis with UI. Therefore, the current study allows more accurate conclusions to be drawn regarding spaying causality.

No clear association was identified between age at spay and UI diagnosis. This finding is supported by some studies (Thrusfield *et al.* 1998, de Bleser *et al.* 2011, Beauvais *et al.* 2012) but not others. A USA study reported higher incidence of UI in bitches that were spayed before 3 months of age (Spain *et al.* 2004) and, in our experience, this is widely used as a justification to postpone spaying. In the current study, only one control was spayed before 3 months of age, with the vast majority of early spaying performed at 5 to 6 months of age. Therefore, a greater number of bitches spayed <3 months would be required to explore this association further. However, it may be that vets are reluctant to advise early spay due to the findings of Spain *et al.* (2004). A more recent study reported that the timing of spay may be of clinical importance in dogs weighing >25 kg but not for those

Table 2. Final multivariable model for risk factors associated with incidence of urinary incontinence in bitches under primary veterinary care in the UK – including “spay status” variable. (n=2135)

Variable	Category	Odds ratio	95% CI	Variable P-value
Spay status	Entire	Base		<0.001
	Spayed	3.01	2.23 to 4.05	
Age (years)	<3.0	Base		<0.001
	3.0 to <6.0	0.64	0.42 to 0.99	
	6.0 to <9.0	0.93	0.61 to 1.42	
	9.0 to <12.0	1.67	1.09 to 2.55	
	≥12.0	4.06	2.64 to 6.24	
Bodyweight (kg)	<10.0	Base		<0.001
	10.0 to <20.0	1.89	1.27 to 2.81	
	20.0 to <30.0	2.54	1.66 to 3.87	
	≥30.0	3.18	1.98 to 5.12	
Breed	Not recorded	0.30	0.17 to 0.55	<0.001
	Crossbreed – non-designer	Base		
	Hungarian vizsla	11.40	1.43 to 90.97	
	Dobermann	6.44	1.13 to 36.60	
	Weimaraner	5.83	1.25 to 27.28	
	Boxer	2.98	1.23 to 7.18	
	Bichon frise	1.91	0.67 to 5.47	
	Border collie	1.45	0.81 to 2.60	
	English springer spaniel	1.40	0.75 to 2.59	
	German shepherd dog	1.33	0.64 to 2.79	
	West Highland white terrier	1.15	0.54 to 2.43	
	Cavalier King Charles spaniel	1.07	0.50 to 2.30	
	Yorkshire terrier	0.94	0.42 to 2.10	
	Jack Russell terrier	0.93	0.52 to 1.67	
	Purebred – other	0.58	0.40 to 0.84	
	Cocker spaniel	0.55	0.28 to 1.11	
	Labrador retriever	0.54	0.32 to 0.91	
	Crossbreed – designer	0.42	0.20 to 0.87	
	French bulldog	0.40	0.09 to 1.77	
	Staffordshire bull terrier	0.20	0.10 to 0.41	
	Chihuahua	0.15	0.02 to 1.14	
	Shih-tzu	0.12	0.02 to 0.89	
Vet group	1	Base		0.065
	2	0.77	0.59 to 0.99	
	3	0.20	0.02 to 2.39	

<15 kg (Byron *et al.* 2017). Bitches in the “Not recorded” category for the age at spay variable had increased odds of UI diagnosis compared with those spayed at 6 to <12 months. The majority of bitches in this category were ≥5 years; therefore, this is likely an effect of age, with this information not recorded for older dogs that have an incomplete history (if changed vets, been rehomed and so forth).

Demographic associations were evaluated primarily in the current study to adjust for confounding in order to better understand the main spaying associations. Nonetheless, the associations reported were consistent with previous work. Breeds predisposed to UI in the current study concur with those identified in previous studies, where the Dobermann, Weimaraner and boxer were also identified as higher-risk breeds (Holt & Thrusfield 1993, Arnold 1997, O'Neill *et al.* 2017). The Hungarian vizsla has not previously been identified as being at increased risk of UI. This may indicate a changing risk or demographics for this breed over time, but only a small number of Hungarian vizslas overall were included in this study. The CIs explain the level of uncertainty as a result of varying breed numbers (see Tables 2 & 3). Previous studies focusing on the few most common breeds have been limited by this restriction. This same reasoning could be applied to the Irish setter, which has previously been identified as one

of the highest-risk breeds (Holt & Thrusfield 1993, O'Neill *et al.* 2017), but only three cases were observed in the current study and so this breed was not retained as an individual breed in the breed analysis. Breeds at reduced odds included the Labrador retriever, Staffordshire bull terrier and shih-tzu. Crossbreeds were split into designer and non-designer breeds as strong breed associations have been identified previously (Holt & Thrusfield 1993, O'Neill *et al.* 2017); crosses of two purebreds may perhaps have been at greater risk than dogs with greater mixed parentage. Separating the crossbreeds into these two groups allowed us to separate out and test these groups separately. It was found, however, that the designer crossbreeds had reduced risk of UI compared with the non-designer crossbreeds. Designer crossbreeds have become increasingly popular in recent years, and this group of dogs was generally younger than the non-designer crossbreeds in this study. Therefore, designer crossbreeds would not have had as long to develop UI compared with non-designer crossbreeds, which may explain the protective effect, although age was accounted for in the multivariable model and thus should have accounted for this potential confounding.

Bitches weighing ≥10.0 kg had increased odds of developing UI compared with those <10.0 kg, with bitches ≥30.0 kg having the highest odds. These results are comparable with those of

Table 3. Descriptive statistics and univariable logistic regression results for risk factors associated with incidence of urinary incontinence in spayed-only bitches under primary veterinary care in the UK (n=1254)

Variable	Category	Control	Case	Odds ratio	95% CI	Variable P-value
Age at spay (months)	<6	55	13	1.39	0.72 to 2.70	<0.001
	6 to <12	128	31	Base		
	12 to <24	119	25	1.04	0.54 to 2.00	
	≥24	161	37	1.14	0.62 to 2.09	
	Not recorded	438	246	2.78	1.66 to 4.66	
Age (years)	<3.0	131	41	Base		<0.001
	3.0 to <6.0	279	61	0.70	0.45 to 1.09	
	6.0 to <9.0	245	72	0.94	0.61 to 1.46	
	9.0 to <12.0	154	89	1.85	1.19 to 2.86	
	≥12.0	92	89	3.09	1.96 to 4.88	
Bodyweight (kg)	<10.0	312	60	Base		<0.001
	10.0 to <20.0	246	108	2.28	1.60 to 3.26	
	20.0 to <30.0	140	108	4.01	2.76 to 5.83	
	≥30.0	101	62	3.19	2.10 to 4.86	
	Not recorded	102	14	0.71	0.38 to 1.33	
Breed	Crossbreed – non-designer	220	114	Base		<0.001
	Hungarian vizsla	1	6	11.58	1.38 to 97.34	
	Weimaraner	1	7	13.51	1.64 to 111.14	
	Boxer	4	10	4.83	1.48 to 15.72	
	German shepherd dog	14	15	2.07	0.96 to 4.43	
	English springer spaniel	23	22	1.85	0.99 to 3.46	
	Border collie	26	24	1.78	0.98 to 3.24	
	Cavalier King Charles spaniel	25	10	0.77	0.36 to 1.66	
	Labrador retriever	64	24	0.72	0.43 to 1.22	
	Yorkshire terrier	22	7	0.61	0.26 to 1.48	
	Jack Russell terrier	54	15	0.54	0.29 to 0.99	
	West Highland white terrier	25	7	0.54	0.23 to 1.29	
	Cocker spaniel	39	12	0.59	0.30 to 1.18	
	Purebreed – other	230	59	0.50	0.34 to 0.71	
	Crossbreed – designer	55	10	0.35	0.17 to 0.71	
	Staffordshire bull terrier	66	9	0.26	0.13 to 0.55	
	Shih-tzu	31	1	0.06	0.01 to 0.46	
Vet group	1	562	236	Base		0.225
	2	332	115	0.83	0.64 to 1.07	
	3	7	1	0.34	0.04 to 2.78	

Table 4. Results for “age at spay” as a risk factor for incidence of urinary incontinence in spayed-only bitches under primary veterinary care in the UK

Variable	Category	Odds ratio	95% CI	Variable P-value
Age at spay (months)	<6	1.51	0.72 to 3.15	<0.001
	6 to <12	Base		
	12 to <24	0.91	0.45 to 1.88	
	≥24	1.10	0.54 to 2.25	
	Not recorded	2.60	1.40 to 4.85	

The multivariable model included age, breed, bodyweight and vet group as confounders (n=1254)

previous studies in which increasing bodyweight was identified as being associated with UI (Okkens *et al.* 1997, Stocklin-Gautschi *et al.* 2001, Angioletti *et al.* 2004, de Bleser *et al.* 2011, Forsee *et al.* 2013, O'Neill *et al.* 2017). A recent study highlighted that breed and bodyweight are highly correlated, therefore identifying which phenotypic characteristic represents the major association can be challenging (O'Neill *et al.* 2017). It was reported that individual breeds weighing at or above the breed average had increased odds of UI compared with bitches below the breed average, supporting the finding that bodyweight, in addition to breed, is a risk factor for UI (O'Neill *et al.* 2017). In the current study, breeds with increased odds of UI were mainly large

or giant breeds, consistent with other studies (Holt & Thrusfield 1993, O'Neill *et al.* 2017).

Bitches aged ≥9.0 years had increased odds of UI compared with those <3.0, which is in agreement with previous studies (de Bleser *et al.* 2011, O'Neill *et al.* 2017). Bitches aged 3.0 to <6.0 had reduced odds of UI compared with those <3.0, which is in contrast to previous findings (de Bleser *et al.* 2011, O'Neill *et al.* 2017). This discrepancy is most likely due to differences in study definition. A previous case-control study focussed solely on USMI, which is less common in juvenile bitches, whereas a broader definition was used in the current study, which included all causes of UI (both congenital and acquired) (de Bleser *et al.* 2011). Therefore, the group of bitches with UI that were aged <3.0 years is likely to have included both congenital and acquired causes (or in combination), hence increasing the number of cases in this age group.

There were limitations to the current study. The age and bodyweight of cases were taken as those recorded at UI diagnosis, whereas the age and bodyweight of controls were taken at the end of the study period. This allowed all information to be collected at one point in time but may have biased towards older and potentially heavier controls. However, as UI was associated with increased age and bodyweight, this means that the risk may be even higher than reported in the current study. The age at

diagnosis of UI cases was significantly greater than the age of controls, although the distribution of ages of cases and controls demonstrated good overlap such that there was no separation of data (Dohoo *et al.* 2009). As such, the multivariable model was able to adjust efficiently for the age at diagnosis such that the effects of other variables were reported after controlling for current animal age. Nonetheless, this adjustment did not take account of those control dogs that may have subsequently gone on to develop UI after the study period. Given that the estimated prevalence of UI was approximately 3.14% (O'Neill *et al.* 2017), there was a relatively low risk of control misclassification. Hence, this potential misclassification of controls was likely to have minimally altered the estimates of other variables adjusted for age, such that the results of the final modelling should be robust to these effects.

There are difficulties in applying a case definition to primary care practice data. Bitches with therapeutically responsive UTIs were excluded, but these dogs may have had low-grade UI that worsened with the UTI. The diagnosis of UI in these cases was uncertain, with insufficient evidence available to include them as cases, and as such, the current study may have underestimated the frequency of UI, particularly of subclinical disease. Conversely, as a presumptive diagnosis of USMI is often made, the lack of diagnosis or ruling out contributory or other causes of UI could lead to the overestimation of USMI. The study included all cases diagnosed with UI and did not attempt to categorise them into congenital, anatomic or acquired subsets. It is acquired UI that has been associated previously with neutering (Holt 1985); therefore, the association may be even greater in this subset. The median age that bitches were diagnosed with UI in the current study was 9.1 years, suggesting that the majority of UI cases were acquired rather than congenital.

There were differences in the proportion of cases from each of the three veterinary groups. This variation may have reflected differences in attending populations, diagnostic protocols and management, spaying approaches or other differences. Variation between the veterinary groups was accounted for during the modelling by forcing vet group in as a fixed effect. The surgical method of spay was not reliably recorded and thus not evaluated in the study. Attempts were made to extract data on the stated cause of UI and duration of UI before diagnosis but this information was often non-specific and inconsistently reported in the EPR and therefore was not deemed sufficiently reliable to include in the analysis.

Using stepwise selection to build a multivariable model can be problematic, affecting both interpretation and prediction. However, a manual backward elimination stepwise approach using the variable likelihood ratio test P values as the elimination criteria was adopted to minimise limitations of model development, and model fit and predictive ability were assessed (Dohoo 2010). Category Wald P-values were removed, and only the final variable likelihood ratio test P values were retained when building the model. We used a study sample based on prestudy power calculations. It should be noted that data on age at spay were missing for a large number of cases and controls, which reduced the statistical power to detect an association and

may have introduced some biases. Despite this, the volume of data available still achieved the prestudy power calculation. It was not possible to be sure the data were missing at random; therefore, expanding the case finding would not necessarily have improved the representativeness of any estimates reported. Future studies using a cohort study design may be able to overcome this limitation.

In conclusion, Spayed bitches had increased odds of UI compared with entire bitches. However, there was no clear trend between age at spay and UI diagnosis. This suggests that it is spay per se, rather than the age at spay, that is the dominant factor. These results can assist clinicians in making recommendations on spaying while taking other risk factors for UI such as breed into account.

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Conflict of interest

The authors have no conflict of interest to declare.

Consent for publication

Authorised for publication.

Availability of data and material

The datasets generated and analysed during the current study are not publicly available due to their use in ongoing primary research, but subsections may be made available from the corresponding author on reasonable request.

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